

What is claimed is:

1. A peptide of formula VI,



5 wherein m and n are each independently 0 or 1;

A is a natural or unnatural amino acid residue having a side chain comprising at least one H-bond acceptor moiety and at least one H-bond donor moiety;

each of **B** and **D** is independently an amino acid residue selected from arginine, glycine, citrulline, glutamine, serine, lysine, asparagine, isoleucine and alanine;

10 **C** is a natural or unnatural amino acid residue having a branched or unbranched C₁-C₆ alkylene side chain optionally containing a H-bond donor or a H-bond acceptor moiety; and
E is a natural or unnatural amino acid residue having an aryl or heteroaryl side chain.

2. A peptide according to claim 1, wherein the H-bond donor moiety is a functional
 15 group

containing an N-H or O-H group, and the H-bond acceptor moiety is a functional group containing C=O or N.

3. A peptide according to claim 1, wherein **C** is selected from group consisting of
 20 alanine, valine, leucine, β-leucine, β-OH-β-leucine, isoleucine, aspartate, glutamate, asparagine, glutamine, lysine, arginine, serine and threonine.

4. A peptide according to claim 2 wherein **C** is selected from the group consisting of
 25 alanine, valine, leucine, β-leucine, β-OH-β-leucine, isoleucine, aspartate, glutamate, asparagine, glutamine, lysine, arginine, serine and threonine.

5. A peptidomimetic according to claim 1, wherein **C** is leucine, isoleucine, β-leucine, β-OH-β-leucine, or asparagine.

30 6. A peptide according to claim 1 wherein **B** is arginine, citrulline, glutamine, serine, or lysine.

7. A peptide according to claim 1, wherein **D** is asparagine, isoleucine or alanine.
8. A peptide according to claim 1, wherein **A** is arginine, glutamine, citrulline.
- 5 9. A peptide according to claim 1, wherein **E** is selected from the group consisting of phenylalanine, *para*-fluorophenylalanine, *meta*-fluorophenylalanine, *ortho*-chlorophenylalanine, *para*-chlorophenylalanine, *meta*-chlorophenylalanine, thienylalanine, N-methylphenylalanine, homophenylalanine (Hof), tyrosine, tryptophan, 1-naphthylalanine (1Nal), 2-naphthylalanine (2Nal), and biphenylalanine (Bip) or (Tic).
- 10 10. A peptide according to claim 1, wherein **E** is phenylalanine, *para*-fluorophenylalanine, *meta*-fluorophenylalanine, *ortho*-chlorophenylalanine, *para*-chlorophenylalanine, *meta*-chlorophenylalanine, thienylalanine, or N-methylphenylalanine.
- 15 11. A variant of a peptide according to any one of claims 3 to 10 wherein:
- (a) **A** is unchanged or conservatively substituted;
- (f) **B** is substituted by any amino acid capable of providing at least one site for participating in hydrogen bonding;
- (g) **C** is unchanged or conservatively substituted;
- 20 (h) **D** is unchanged or conservatively substituted;
- (i) **E** is unchanged or substituted by any aromatic amino acid.
12. A peptide according to claim 1, wherein m and n are both 1.
- 25 13. A peptide according to claim 11, wherein m and n are both 1.
14. A peptide according to claim 1, wherein m is 1 and n is 0.
15. A peptide according to claim 11, wherein m is 1 and n is 0.
- 30 16. A peptide according to claim 1, wherein m is 0 and n is 1.

17. A peptide according to claim 11, wherein m is 0 and n is 1.

18. A peptide according to claim 1, wherein m and n are both 0.

5 19. A peptide according to claim 11, wherein m and n are both 0.

20. A peptide according to claim 1, wherein the peptide is selected from the group consisting of

Compound No.	SEQ ID No.	N-terminus						C-terminus
VI.1	461	H	Arg	Arg	Leu	Asn	p-F-Phe	NH ₂
VI.2	462	Ac	Arg	Arg	Leu	Asn	p-F-Phe	NH ₂
VI.3	463	H	Arg	Arg	Ile	Asn	p-F-Phe	NH ₂
VI.4	464	Ac	Arg	Arg	Ile	Asn	p-F-Phe	NH ₂
VI.5	377	H	Arg	Arg	Leu	Ile	Phe	NH ₂
VI.6	465	Ac	Arg	Arg	Leu	Ile	Phe	NH ₂
VI.7	466	H	Arg	Arg	Leu	Ala	p-F-Phe	NH ₂
VI.8	467	Ac	Arg	Arg	Leu	Ala	p-F-Phe	NH ₂
VI.9	468	H	Gln	Arg	Leu	Ile	p-F-Phe	NH ₂
VI.10	469	H	Cit	Arg	Leu	Ile	p-F-Phe	NH ₂
VI.11	470	H	Arg	Cit	Leu	Ile	p-F-Phe	NH ₂
VI.12	471	H	Arg	Gln	Leu	Ile	p-F-Phe	NH ₂
VI.13	472	H	Gln	Ser	Leu	Ile	p-F-Phe	NH ₂
VI.14	473	H	Cit	Cit	Leu	Ile	p-F-Phe	NH ₂
VI.15	474	H	Cit	Gln	Leu	Ile	p-F-Phe	NH ₂
VI.16	475	H	Arg	Cit	Leu	Ala	p-F-Phe	NH ₂
VI.17	476	H	Arg	Gln	Leu	Ala	p-F-Phe	NH ₂
VI.18	477	H	Arg	Cit	Leu	Asn	p-F-Phe	NH ₂
VI.19	478	H	Arg	Gln	Leu	Asn	p-F-Phe	NH ₂
VI.20	479	H	Cit	Cit	Leu	Asn	p-F-Phe	NH ₂
VI.21	480	Ac	Arg	Arg	β-Leu	p-F-Phe	NH ₂	
VI.22	481	Ac	Arg	Ser	β-Leu	p-F-Phe	NH ₂	
VI.23	482	Ac	Arg	Arg	β-Leu	m-F-Phe	NH ₂	
VI.24	483	Ac	Arg	Ser	β-Leu	m-F-Phe	NH ₂	
VI.25	484	Ac	Arg	Arg	β-Leu	o-Cl-Phe	NH ₂	
VI.26	485	Ac	Arg	Ser	β-Leu	o-Cl-Phe	NH ₂	
VI.27	486	Ac	Arg	Arg	β-Leu	m-Cl-Phe	NH ₂	
VI.28	487	Ac	Arg	Ser	β-Leu	m-Cl-Phe	NH ₂	
VI.29	488	Ac	Arg	Arg	β-Leu	p-Cl-Phe	NH ₂	
VI.30	489	Ac	Arg	Arg	β-Leu	Thi	NH ₂	

VI.31	490	H	Arg	Ser	β -Leu	m-F-Phe	NH ₂
VI.32	491	H	Arg	Arg	β -Leu	p-F-Phe	NH ₂
VI.33	492	H	Arg	Arg	β -Leu	m-F-Phe	NH ₂
VI.34	493	H	Arg	Arg	β -Leu	o-Cl-Phe	NH ₂
VI.35	494	H	Arg	Arg	β -Leu	m-Cl-Phe	NH ₂
VI.36	495	H	Arg	Arg	β -Leu	Thi	NH ₂
VI.37	496	H	Arg	Ser	β -Leu	o-Cl-Phe	NH ₂
VI.38	497	Ac	Arg	Arg	β -Leu	Phe	NH ₂
VI.39	498	Ac	Arg	Ser	β -Leu	Phe	NH ₂
VI.40	499	Ac	Arg	Arg	β -Leu	NMePhe	NH ₂
VI.41	500	Ac	Arg	Ser	β -Leu	NMePhe	NH ₂
VI.42	501	Ac	Leu	Asn		p-F-Phe	NH ₂
VI.43	502	H	Arg	Arg	β -OH- β -Leu	p-F-Phe	NH ₂
VI.44	503	H	Cit	Cit	β -OH- β -Leu	p-F-Phe	NH ₂ ; and
VI.45	504	Ac	Arg	Lys ^b	Leu	Phe	Gly ^b

wherein *b* denotes a carboxamide bond between the Lys ϵ -amino group and Gly carboxyl group.

21. A peptide according to claim 11, or variant thereof, which is selected from the following:

H- Arg Arg Leu Asn Phe NH₂
H- Arg Arg Leu Asn pFF NH₂
H- Arg Arg Leu Asn mClF NH₂
H- Arg Arg Leu Ala pFF NH₂
H- Arg Arg Ile Asn pFF NH₂
H- Arg Arg Ile Ala pFF NH₂
H- Arg Lys Leu Ala pFF NH₂
H- Arg Arg Leu Asn pFF NH₂
H- Arg Arg Ile Asn pFF NH₂
H- Arg Arg Leu Ile pFF NH₂

22. A peptide according to claim 1, wherein the N-terminal is acylated.

23. A peptide according to claim 1, wherein the peptide is
- (a) modified by substitution of one or more natural or unnatural amino acid residues by the corresponding D-stereomer;
 - (b) a chemical derivative of the peptide;
 - 5 (c) a cyclic peptide derived from the peptide or from a peptide derivative;
 - (d) a dual peptide;
 - (e) a multimer of peptides;
 - (f) any of said peptides in the D-stereomer form; or
 - (g) a peptide in which the order of the final two residues at the C-terminal end is reversed.

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24. A pharmaceutical composition comprising a peptide, according to claim 1, wherein the peptide is admixed with a pharmaceutically acceptable diluent excipient or carrier.

25. Use of a peptide defined in claim 1 in the preparation of a medicament for use in (a)
- 15 inhibition of CDK2 or (b) in the treatment of proliferative disorders such as cancers and leukaemias where inhibition of CDK2 would be beneficial.

26. An assay for identifying candidate substances capable of binding to a cyclin associated with a G1 control CDK enzyme and/or inhibiting said enzyme, comprising;

- 20 (a) bringing into contact a peptide of claim 1, said cyclin, said CDK and said candidate substance, under conditions wherein, in the absence of the candidate substance being an inhibitor of interaction of the cyclin/CDK interaction, the peptidomimetic would bind to said cyclin; and
- (b) monitoring any change in the expected binding of the peptide and the cyclin.

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27. An assay for the identification of compounds that interact a cyclin or a cyclin when complexed with the physiologically relevant CDK, comprising:

- (a) incubating a candidate compound and a peptide according to claim 1, or a variant thereof, and a cyclin or cyclin/CDK complex,
- 30 (b) detecting binding of either the candidate compound or the peptide with the cyclin.

28. An assay according to claim 26 wherein the cyclin is selected from cyclin A, cyclin E or cyclin D.
- 5 29. An assay according to claim 27 wherein the cyclin is selected from cyclin A, cyclin E or cyclin D.
30. An assay according to claim 26 wherein the cyclin is cyclin A.
- 10 31. An assay according to claim 27 wherein the cyclin is cyclin A.
32. An assay according to claim 26, comprising use of a three dimensional model of a cyclin and a candidate compound.
- 15 33. An assay according to claim 27, comprising use of a three dimensional model of a cyclin and a candidate compound.
34. An assay according to claim 26, wherein at least one of the assay components is bound to a solid phase.
- 20 35. An assay according to claim 27, wherein at least one of the assay components is bound to a solid phase.
36. An assay according to claim 34, wherein the peptidomimetic is labeled such as to emit
25 a signal when bound to said cyclin.
37. An assay according to claim 35, wherein the peptidomimetic is labeled such as to emit a signal when bound to said cyclin.
- 30 38. An assay according to claim 34, wherein the cyclin is labeled such as to emit a signal when bound to the peptide.

39. An assay according to claim 35, wherein the cyclin is labeled such as to emit a signal when bound to the peptide.

40. An assay according to claim 26, wherein one of the assay components is labeled with a fluorescence emitter and the signal is detected using fluorescence polarisation techniques.

41. An assay according to claim 27, wherein one of the assay components is labeled with a fluorescence emitter and the signal is detected using fluorescence polarisation techniques.

42. A method of using a cyclin in a drug screening assay comprising:

(a) selecting a candidate compound by performing rational drug design with a three-dimensional model of said cyclin, wherein said selecting is performed in conjunction with computer modeling;

(b) contacting the candidate compound with the cyclin; and

(c) detecting the binding of the candidate compound for the cyclin groove; wherein a potential drug is selected on the basis of its having a greater affinity for the cyclin groove than that of a peptide according to claim 1.

43. A method according to any of claims 26, 27, 41, or 42, wherein the method of detection comprises monitoring G0 and/or G1/S cell cycle, cell cycle-related apoptosis, suppression of E2F transcription factor, hypophosphorylation of cellular pRb, or in vitro anti-proliferative effects.

44. An assay according to claim 43, wherein the method of detection comprises monitoring G0 and/or G1/S cell cycle, cell cycle-related apoptosis, suppression of E2F transcription factor, hypophosphorylation of cellular pRb, or in vitro anti-proliferative effects.

45. A peptide of formula I,

$$N_1DFYHSKRRLIFN_2 \text{ (formula I) (SEQ ID No. 4),}$$

comprising the motif XLXF (SEQ ID No. 11);

wherein N_1 and N_2 are independently a natural or non-natural amino acid or nothing;

or the peptide of formula I having up to 8 amino acid residues deleted from the N-terminal

end; and variants thereof wherein at least one amino acid residue is replaced by an alternative natural or non-natural replacement amino acid residue, with the proviso that the motif XLXF (SEQ ID No. 11), is retained;

wherein X refers to any natural or unnatural amino acid.

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46. A peptide of formula,

DFYHSKRRLIF (SEQ ID No. 1), comprising the motif XLXF, or such a peptide:

- (i) bearing a further amino acid residue at either end; and,
- (ii) having up to 7 amino acid residues deleted from the N-terminal end;

10 and variants thereof wherein at least one amino acid residue is replaced by an alternative natural or unnatural replacement amino acid residue, with the proviso that the motif XLXF (SEQ ID No. 11) is retained, wherein the peptide of SEQ ID No. 1 is modified by at least one of; deletion, addition or substitution of one or more amino acid residues, or by substitution of one or more natural amino acid residues by the corresponding D-stereomer or by a non-natural
15 amino acid residue, chemical derivatives of the peptides, cyclic peptides derived from the peptides or from the peptide derivatives, dual peptides, multimers of the peptides and any of said peptides in the D-stereomer form, or the order of the final two residues at the C-terminal end are reversed.

20 47. A peptide of the formula,

$X_1X_2X_3RX_4LX_5F$ (SEQ ID No. 2);

wherein X_1 , X_3 , X_4 and X_5 may be amino acid and X_2 is serine or alanine; and variants thereof, wherein

- (a) X_1 is deleted or is any amino acid;
- 25 (b) X_2 is serine or alanine or a straight or branched chain amino acid;
- (c) X_3 is a basic amino acid or straight chain aliphatic amino acid;
- (d) R is unchanged or conservatively substituted by a basic amino acid;
- (e) X_4 is an amino acid that is capable of providing at least one site for participating in hydrogen bonding;
- 30 (f) L is unchanged or conservatively substituted;
- (g) X_5 is any amino acid,;or
- (h) F is unchanged or substituted by any aromatic amino acid.

48. A peptide of the formula III or IV,

$H'X_2K'R_1R_2L'X_5F$ (formula III) (SEQ ID No. 3) or

$H'X_2K'R_1R_2L'FX_5$ (formula IV) (SEQ ID No. 189) or a variant thereof,

5 wherein

H' is nothing, His, D-His, Ala, Thi, Hse, Phe, or Dab;

X_2 is Ala, Ser, Abu, Val;

K' is Lys, Arg, or Abu;

R_1 is Arg, Lys, or Gln;

10 R_2 is Arg, forms a cyclic peptide with the C-terminal residue, Ser, or Cit;

L' is Leu or Ile;

X_5 is Ile, Leu, Gly, or Ala; and

F' is Phe, para-fluoroPhe, meta-fluoroPhe, L-Psa, 2-Nap,Dhp, or D-Psa.

15 49. A peptide of formula V, $RX_6X_7X_8X_9$ (SEQ ID No. 293),

wherein

X_6 is arginine, serine or lysine;

X_7 is leucine, isoleucine or valine;

X_8 is asparagine, alanine, glycine or isoleucine; and

20 X_9 is phenylalanine;

or variants thereof.

50. A peptide according of the formula,

$RX_6X_7X_8X_9$ (SEQ ID No. 293) or variants thereof,

25 wherein;

(a) R is unchanged or conservatively substituted by a basic amino acid;

(b) X_6 is substituted by any amino acid capable of providing at least one site for participating in hydrogen bonding;

(c) X_7 is unchanged or conservatively substituted;

30 (d) X_8 is unchanged or conservatively substituted; and

(e) X_9 is unchanged or substituted by any aromatic amino acid.

51. A peptide according to formula V,

$RX_6X_7X_8X_9$ (SEQ ID No. 293) or variants thereof,

wherein:

(a) R is replaced by either a basic residue such as lysine or an uncharged natural or
5 unnatural amino acid residue, such as citrulline (Cit), homoserine, histidine, norleucine (Nle),
or glutamine;

(b) X_6 is replaced by a natural or unnatural amino acid residue such as asparagine,
proline, aminoisobutyric acid (Aib) or sarcosine (Sar), or an amino acid residue capable of
forming a cyclic linkage such as ornithine;

10 (c) X_7 is replaced with a natural or unnatural amino acid residue having a slightly
larger aromatic or aliphatic side chain, such as norleucine, norvaline, cyclohexylalanine
(Cha), phenylalanine or 1-naphthylalanine (1Nal);

(d) X_8 is replaced with a natural or unnatural amino acid residue having a slightly
larger aromatic or aliphatic side chain, such as norleucine, norvaline, cyclohexylalanine
15 (Cha), phenylalanine or 1-naphthylalanine (1Nal); and

(e) X_9 is replaced with a natural or unnatural amino acid such as leucine,
cyclohexylalanine (Cha), homophenylalanine (Hof), tyrosine, para-fluorophenylalanine
(pFPhe), meta-fluorophenylalanine (mFPhe), tryptophan, 1-naphthylalanine (1Nal), 2-
naphthylalanine (2Nal), meta-chlorophenylalanine (mClPhe), biphenylalanine (Bip) or (Tic).

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